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REVIEW

Pharmacokinetics and pharmacodynamics of the new oral anticoagulants

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Abstract
Dabigatran is the first available oral direct thrombin inhibitor anticoagulant. Absorption of the prodrug, dabigatran etexilate and its conversion to dabigatran is rapid (peak plasma concentrations are reached 4-6 h following surgery, and a further 2 h later). Its oral bioavailability is low, but shows reduced interindividual variability. Dabigatran specifically and reversibly inhibits thrombin, the key enzyme in the coagulation cascade. Studies both in healthy volunteers and in patients undergoing major orthopaedic surgery show a predictable pk/pd profile that allows for fixed-dose regimens. The anticoagulant effect correlates adequately with the plasma concentrations of the drug, demonstrating effective anticoagulation combined with a low risk of bleeding. Dabigatran is mainly eliminated by renal excretion (a fact which affects the dosage in elderly and in moderate-severe renal failure patients), and no hepatic metabolism by cytochrome P450 isoenzymes has been observed, showing a good interaction profile.
Rivaroxaban will probably be the first available oral factor Xa (FXa) direct inhibitor anticoagulant drug. It produces a reversible and predictable inhibition of FXa activity with potential to inhibit clot-bound FXa. Its pharmacokinetic characteristics include rapid absorption, high oral availability, high plasma protein binding and a half-life of aprox. 8 h. Rivaroxaban elimination is mainly renal, but also through faecal matter and by hepatic metabolism. Although the drug has demonstrated moderate potential to interact with strong CYP3A4 inhibitors, it does not inhibit or induce any major CYP450 enzyme.

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Farmacocinética y farmacodinamia de los nuevos anticoagulantes orales

Resumen
Dabigatran es el primer anticoagulante inhibidor directo de la trombina disponible por vía oral. La absorción del profármaco dabigatran etexilato y su conversión a dabigatran es rápida (concentraciones máximas de 4-6 h tras cirugía y 2 h posteriormente) y, pese a la baja biodisponibilidad oral, presenta escasa variabilidad entre individuos. Inhibe específica y reversiblemente la trombina, la enzima llave de la cascada de la coagulación. Los estudios tanto en voluntarios sanos como en pacientes sometidos a cirugía ortopédica mayor muestran un perfil pk/pd predecible, lo que permite regímenes fijos de dosificación. El efecto anticoagulante se correlaciona bien con las concentraciones plasmáticas del fármaco, lo que aúna una efectiva anticoagulación con un bajo riesgo de hemorragia. La excreción es mayoritariamente renal (lo que condiciona su dosificación en pacientes ancianos y con insuficiencia renal), y no sufre metabolismo hepático por el sistema del citocromo P450, por lo que presenta un perfil de fármaco sin grandes problemas de interacción con otros medicamentos.
Rivaroxaban será probablemente el primer fármaco anticoagulante oral inhibidor directo del factor Xa (FXa) disponible. Produce una inhibición reversible y predecible de la actividad del FXa con capacidad de inhibir el FXa ligado al coágulo. Sus características farmacocinéticas incluyen rápida absorción, con elevadas biodisponibilidad y unión a proteínas plasmáticas y semivida de eliminación de, aproximadamente, 8 h. La eliminación es de tipo dual, renal (mayoritaria) y biliar. Aunque ha demostrado tener un potencial moderado de interacción con inhibidores fuertes del citocromo P450-A4, no parece inhibir ni inducir ninguna enzima P450.

Introduction

There are currently various antithrombotic agents used in clinical practice, such as unfractionated heparin (UFH), and related agents, such as low-molecular-weight heparins (LMWH) and the derivative synthetic pentasaccharide fondaparinux, oral anticoagulants (such as warfarin and acenocoumarol), parenteral direct thrombin inhibitors (lepirudin and bivalirudin) or even acetylsalicylic acid (aspirin), the use of which has been demonstrated as effective and safe.[1,2]

However, these treatments have various disadvantages, since, for example, in the case of heparin, it must be administered parenterally and may cause thrombocytopenia (HIT). In addition, it requires strict laboratory monitoring (activated partial thromboplastin time [aPTT]). In the case of LMWH and fondaparinux, its main disadvantage lies in the fact that, aside from its parenteral administration, it must be used with precaution in patients with renal failure. In addition, there is no antidote which can effectively neutralise its activity in the event of haemorrhage. In the case of oral dicumarinic anticoagulants, the disadvantages are that the dosage must be adjusted and periodic laboratory tests must be performed in accordance with international normalized ratio (INR), as well as bearing in mind that the treatment may cause multiple interactions with other drugs and with some foods.[3-5] Despite the vast efforts in the health care industry with respect to the formal registration and appropriate use of the available anticoagulant drugs, the desired results in clinical practice have not been obtained.[6]

These limitations have directed research towards the search of drugs which, administered orally, directly inhibit clearly-defined stages of coagulation, and therefore, reduce the generation of thrombin or directly inhibit the final enzymatic product, thrombin. This antithrombinic action may also modify platelet activation mediated by thrombin, an action that drugs which specifically inhibit platelet function do not have, at least to the degree required to obtain a sufficient level of prevention of arterial thromboembolic disease.[7,8]

Following a period in which pharmacological innovations have been scarce in the field of anticoagulants, new drugs are beginning to emerge which must be demonstrated to be more effective and safer than those used traditionally. In this respect, research has been carried out on new oral anticoagulants which act by means of different mechanisms of action, such as direct thrombin inhibitors and direct factor Xa inhibitors (Figure).[9]

In Spain, a new oral direct thrombin inhibitor has recently been released on the market, the dabigatran etexilate Pradaxa® (Boehringer Ingelheim), for the prevention of venous thromboembolism (VTE) in adults who have undergone hip or knee replacement surgery. Furthermore, the Spanish Agency of Drugs and Healthcare Products has authorised a new oral direct factor Xa inhibitor drug, rivaroxaban (Xarelto®), developed by Bayer HealthCare and Johnson & Johnson Pharmaceutical Research & Development, for the prevention of venous blood clots in patients who have undergone elective total hip replacement or total knee replacement surgery.[7,8]

The main aim of this review is to assess the pharmacodynamic and pharmacokinetic properties of the drugs dabigatran